

What is claimed is:

1. A method for identifying a non-human primate polynucleotide sequence encoding a polypeptide, wherein said polypeptide is or is suspected of being associated with enhanced resistance to hepatitis C virus (HCV) infection in the non-human primate, comprising the steps of:
 - a) comparing non-human primate polypeptide-coding polynucleotide sequences to polypeptide-coding polynucleotide sequences of a human, wherein said non-human has an enhanced resistance to HCV infection relative to the human; and
 - b) selecting a non-human primate polynucleotide sequence that contains a nucleotide change as compared to the corresponding sequence of the human, wherein said change is evolutionarily significant.
2. The method of claim 1 wherein the non-human primate is selected from the group consisting of chimpanzee, bonobo, gorilla and orangutan.
3. The method of claim 2 wherein the non-human primate is chimpanzee.
4. The method of claim 1, wherein the evolutionary significance of the nucleotide change is determined by the ratio of the non-synonymous substitution rate (K_A) to the synonymous rate (K_S) of the nucleotide sequence.
5. The method of claim 4 wherein the K_A/K_S ratio is greater than 1.0.
6. The method of claim 4 wherein the K_A/K_S ratio is about 1.5.
7. The method of claim 1 wherein the non-human polynucleotide sequence is chimpanzee p44 exon 2 or a fragment thereof of between about 18-225 nucleotides and

containing at least one evolutionarily significant nucleotide change.

8. A method of identifying target sites on human p44 exon 2 polypeptide which may be suitable for therapeutic intervention, comprising identifying as target sites those amino acids in the human p44 exon 2 that correspond to chimpanzee p44 exon 2 evolutionarily significant nucleotide changes identified according to the method of claim 1.

9. A method for identifying an agent that may modulate a primate's p44 function, comprising:
10 contacting at least one candidate agent with the primate's p44 polypeptide, or a fragment thereof of 6-75 amino acids having at least one amino acid corresponding to an evolutionarily significant nucleotide change,
wherein said agent is identified by its ability to modulate the p44 function.

15 10. An agent obtained by the method of claim 9.

11. The method of claim 9 wherein said primate is human.

12. The method of claim 11 wherein the modulation of the p44 function is selected from the group consisting of improved microtubule assembly and improved resistance to HCV infection.

13. The method of claim 11 wherein the modulation of the p44 function results in a human function that more closely approximates a chimpanzee p44 function.

25 14. The method of claim 11 wherein said p44 polypeptide corresponds to p44 exon 2 polynucleotide.

15. The method of claim 11 wherein said candidate agent is a small molecule that is

designed to interact with human p44 amino acids so that it forms a complex that mimics the three-dimensional structure of the chimpanzee p44, whereby the human p44 function is modulated.

5 16. The method of claim 11 wherein said candidate agent is a small molecule that is designed to interact with human p44 amino acids so as to modulate the human p44 polypeptide function.

10 17. A method for identifying an agent that modulates expression of a human's p44 polynucleotide, comprising:
contacting at least one candidate agent with the human's p44 polynucleotide promoter,
wherein said agent is identified by its ability to enhance expression of the human p44 polynucleotide.

15 18. A method of targeting a small molecule to human p44 exon 2 comprising:
designing the small molecule to interact with any of the amino acids Arg36, Ser68, Glu71, Gly72, Asp84, Cys95, or Thr106 of SEQ ID NO. 36.

20 19. A human p44 polynucleotide consisting essentially of nucleotides 1 to 457 of SEQ ID NO. 34, or fragments thereof of about 18-225 nucleotides and having at least one human nucleotide that corresponds to a chimpanzee exon 2 evolutionarily significant nucleotide change.

25 20. A human p44 polypeptide consisting essentially of amino acids 1 to 152 of SEQ ID NO. 36, or fragments thereof of about 6-75 amino acids having at least one human amino acid that corresponds to a chimpanzee exon 2 evolutionarily significant nucleotide change.

21. A chimpanzee p44 polynucleotide consisting essentially of nucleotides 1 to 457 of SEQ ID NO. 31, or fragments thereof of about 18-225 nucleotides and having at least one chimpanzee exon 2 evolutionarily significant nucleotide change.

5 22. A chimpanzee p44 polypeptide consisting essentially of amino acids 1 to 152 of SEQ ID NO.33, or fragments thereof of about 6-75 amino acids having at least one amino acid that is encoded by a chimpanzee exon 2 evolutionarily significant nucleotide change.

10 23. A method for correlating evolutionarily significant nucleotide changes in a non-human primate p44 polynucleotide to enhanced HCV resistance in the non-human primate, comprising:

analyzing a functional effect, if any, of the p44 polynucleotide containing the evolutionarily significant nucleotide changes in a suitable model system, wherein
15 presence of a functional effect indicates a correlation between the evolutionarily significant p44 polynucleotide and the enhanced HCV resistance.

24. A method for identifying those evolutionarily significant nucleotide changes in a non-human primate p44 polynucleotide that are responsible for enhanced HCV resistance
20 in the non-human primate, comprising:

analyzing a functional effect, if any, of any one or any combination of evolutionarily significant p44 nucleotides in a suitable model system, wherein presence of a functional effect indicates those nucleotides that are responsible for enhanced HCV
resistance.

25 25. A method of identifying candidate polynucleotides that may be associated with decreased resistance to development of a disease in humans, comprising:

a) comparing the human polynucleotide sequence with the corresponding non-human primate polynucleotide sequence to identify any nucleotide changes; and

b) determining whether said human nucleotide changes are evolutionarily significant, whereby candidate polynucleotides are identified.

26. A method of correlating an evolutionarily significant nucleotide change in the candidate polynucleotide of claim 25 to decreased resistance to development of a disease in humans, comprising the method of claim 25, and further comprising:

analyzing the functional effect of the evolutionarily significant nucleotide change in the candidate polynucleotide in a suitable model system, wherein the presence of a functional effect indicates a correlation between the nucleotide change in the candidate polynucleotide and the decreased resistance to development of the disease in humans.

27. A method of correlating a nucleotide change in a human's mutant or allelic polynucleotide to a decrease in resistance to development of a disease, said mutant or allelic polynucleotide corresponding to at least one of the candidate polynucleotides of claim 25 and said nucleotide change being relative to said candidate polynucleotide, comprising the method of claim 25 and further comprising:

analyzing the functional effect of the mutant or allelic polynucleotide in a suitable model system, wherein the presence of a functional effect indicates a correlation between the nucleotide change in the polynucleotide and the decreased resistance to development of a disease.

28. A method of identifying a human evolutionarily significant polynucleotide that predisposes humans to decreased resistance to development of a disease, comprising the steps of:

a) identifying a polynucleotide that is evolutionarily significant and is associated with a physiological condition in humans relative to a non-human primate; and

b) determining whether an evolutionarily significant nucleotide in the evolutionarily significant polypeptide is associated with decreased resistance to development of the disease.

29. The method of claim 28, wherein the step of identifying the evolutionarily significant polynucleotide comprises:
 - i) comparing the human polynucleotide sequence with the corresponding non-human primate polynucleotide sequence to identify any nucleotide changes; and
 - ii) determining whether said human nucleotide changes are evolutionarily significant, whereby a positively selected polynucleotide is identified.
30. The method of claim 29, wherein the evolutionary significance of a polynucleotide is determined by K_A/K_S analysis.
31. The method of claim 28, wherein the step of determining whether the evolutionarily significant nucleotide change in the polynucleotide is associated with decreased disease resistance, comprises:
 - analyzing the functional effect of the evolutionarily significant nucleotide change in a suitable model system, wherein the presence of a functional effect determines that the nucleotide change is associated with the decreased resistance to development of the disease.
32. The method of claim 28, wherein the evolutionarily significant polynucleotide is BRCA1 exon 11.
33. The method of claim 28, wherein the disease is selected from the group consisting of breast cancer, prostate cancer and ovarian cancer.
34. A method of identifying a mutant or allele of a human evolutionarily significant polynucleotide, said mutant or allele predisposing humans to decreased resistance to development of a disease, comprising the steps of:
 - a) identifying a polynucleotide that is evolutionarily significant and is

associated with a physiological condition in humans relative to a non-human primate; and

b) determining whether said evolutionarily significant polynucleotide has a mutant or allele with a nucleotide change that is associated with the decreased resistance to development of the disease in humans, whereby the mutant or allele of the human

5 evolutionarily significant polynucleotide is identified.

35. The method of claim 34, wherein the step of identifying the evolutionarily significant polynucleotide comprises:

i) comparing the human polynucleotide sequence with the corresponding
10 non-human primate polynucleotide sequence to identify any nucleotide changes; and

ii) determining whether said human nucleotide changes are evolutionarily significant, whereby a positively selected polynucleotide is identified.

36. The method of claim 35, wherein the evolutionary significance of a
15 polynucleotide is determined by K_A/K_S analysis.

37. The method of claim 34, wherein the step of determining whether the mutant or allelic polynucleotide is associated with decreased disease resistance, comprises:

analyzing the functional effect of the nucleotide change in the mutant or allelic
20 polynucleotide in a suitable model system, wherein the presence of a functional effect determines that the nucleotide change in the polynucleotide is associated with the decreased resistance to development of the disease.

38. The method of claim 34, wherein the evolutionarily significant polynucleotide is
25 BRCA1 exon 11.

39. The method of claim 34, wherein the disease is selected from the group consisting of breast cancer, prostate cancer and ovarian cancer.

30 40. A diagnostic method to determine whether a human patient is predisposed to

decreased resistance for the development of a disease, comprising the method of claim 34 and further comprising:

- 5 assaying the patient's nucleic acids for the presence of the mutation or allele of the evolutionarily significant polynucleotide, whereby the presence of the nucleotide change in the polynucleotide is diagnostic for a predisposition for decreased resistance to the development of the disease.

41. The method of claim 40, wherein the polynucleotide is BRCA1 exon 11.

- 10 42. The method of claim 39, wherein the disease is selected from the group consisting of breast cancer, prostate cancer and ovarian cancer.

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